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Impact of IVDR on patient enrichment in ongoing trials

A Boehringer Ingelheim case study

Fabian Iltzsche | 20 Oct 2025 | EBF IVDR Roadshow

Life forward

Systemic Sclerosis (SSc) overview and unmet needs
Chronic disease with high burden – Opportunity for disease-altering interventions

Disease characteristics

SSc typically begins with vascular symptoms and progresses to fibrosis of skin and multiple internal organs

Prevalence	• **Rare** disease affecting ~2 million people worldwide • **Incidence** of 151 / million / year (15.1 per 100,000 in the US and 6.6 per 100,000 in Japan) • Over 80% of SSc patients are **women**
Severity	• **Skin and visceral organ fibrosis** drive morbidity and mortality • **Highest case mortality rate** among connective tissue diseases ○ 5-yr survival 84% in dcSSc and 93-96% in lcSSc • Significant impact on Quality of Life
Treatment	• No disease-modifying SoC – **substantial unmet need** • Patients managed symptomatically

Disease burden and unmet needs are high

Disease progression is unpredictable

Organ involvement can lead to mortality

Patients fear physical disability and uncertain future

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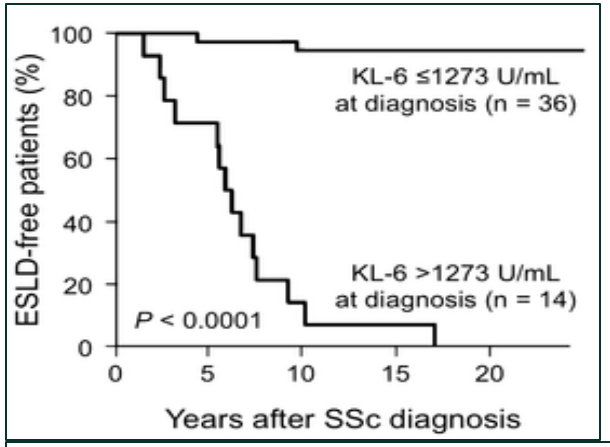
Rationale for KL-6 (Krebs von den Lungen) evaluation in SSc patients

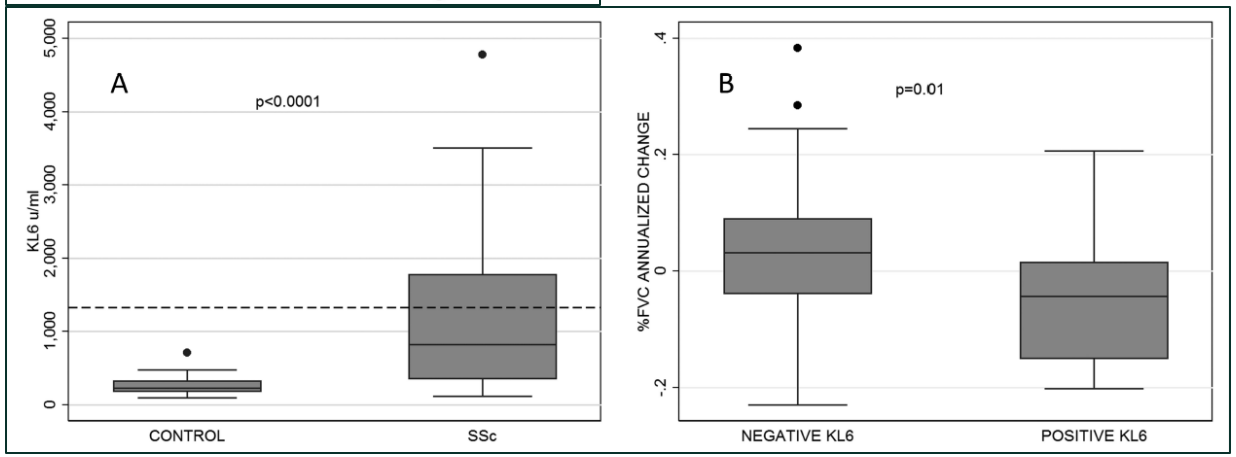
KL-6: A biomarker of disease progression in ILD including SSc-ILD

- Levels of KL-6 are elevated in patients with SSc-ILD compared to those without ILD
- Higher levels of KL-6 indicate
  - Ongoing lung injury and fibrosis
  - Disease progression - a decline in lung function or a greater risk of disease progression
- Potential biomarker prognostic of disease progression decline for SSc-ILD
- <u>Hypothesis</u>: KL-6 biomarker has the potential to be utilized as part of the patient selection criteria in clinical trials in SSc/SSc-ILD

Increased levels of KL-6 (cutoff of 1273 U/ml) are associated with a higher rate of decline in FVC in SSc patients



Kuwana et al 2016; J Rheumatol 43:1825



Salazar et al 2018. J Rheumatol 45: 1153

SSc-ILD: Systemic Sclerosis Interstitial Lung Disease, FVC: Forced vital capacity; ESLD: end stage lung disease, ESR: Erythrocyte sedimentation rate

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Clinical Study CT No. 2022-500332-11-00 in SSc: VITALISScE™

A Study in People With Systemic Sclerosis to Test Whether Avenciguat (BI 685509) Has an Effect on Lung Function and Other Systemic Sclerosis Symptoms (VITALISScE™)

ClinicalTrials.gov ID NCT05559580

Sponsor Boehringer Ingelheim

Information provided by Boehringer Ingelheim (Responsible Party)

Last Update Posted 2024-10-03

-> Running in 37 countries worldwide

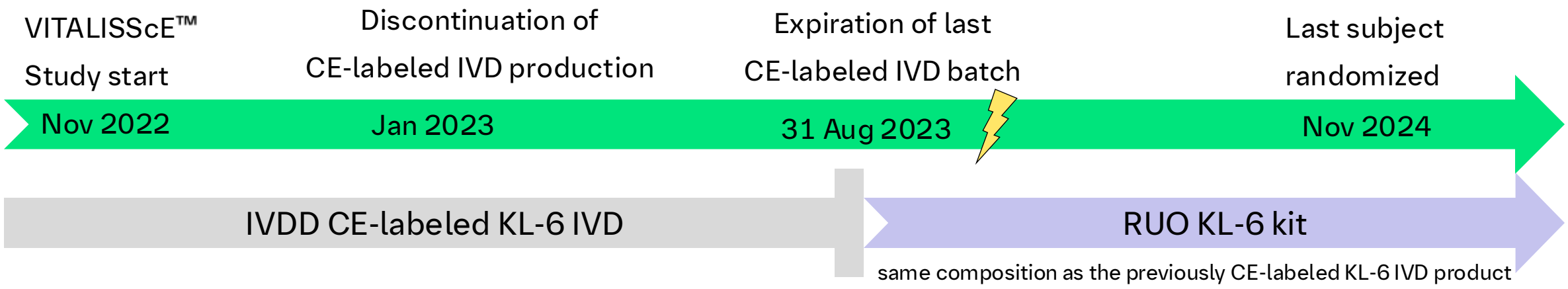
Patient screening and inclusion criteria

- Patients are being screened for ESR, CRP and KL-6
- Each biomarker captures a distinct patient segment
- Patients with KL-6 levels ≥ 1000 U/ml are randomized into the study

ESR: Erythrocyte sedimentation rate CRP: C-reactive protein

Commercial KL-6 Assay details to support the VITALISScE™ study

- KL-6 is approved as diagnostic marker for ILD in Japan since 1999
- For the assessment of KL-6 a CE-labeled IVD kit (under IVDD), manufactured by a Japanese multinational biotechnology company is used
- IVD kit used in previous Boehringer studies with good (scientific) performance
- The central analysis with this kit is performed at a CRO in Germany for the VITALISScE™ study



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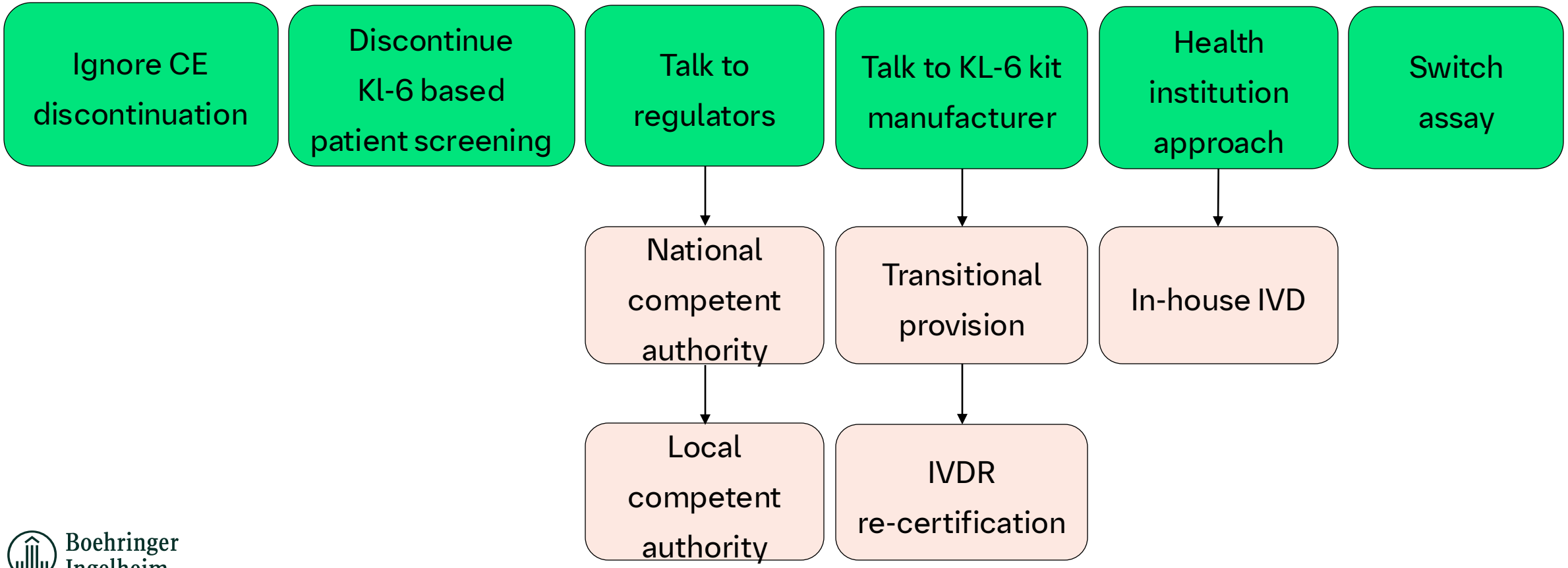
Problem Statement

How to continue to screen EU patients based on KL-6 in ongoing study w/o CE-labeled assay in an IVDR compliant way?



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Option 1: Ignore CE discontinuation

Commercial assay

IVD_GER

2FT05TE

In Vitro Diagnostic Use

INTENDED USE

For *in vitro* diagnostic use with the [redacted] System for the quantitative measurement of a sialylated carbohydrate antigen, KL-6 in human serum or plasma. This product is for professional use only.

RUO_GER

B34155 v0

For research use only. Not for use in diagnostic procedures.

INTENDED USE

For research use with the automated [redacted] System for the quantitative measurement of a sialylated carbohydrate antigen, KL-6 in human serum or plasma. This product is not for use in diagnostic procedures, for 'Research Use Only'. This product is for professional use only.

- composition of RUO assay kit after CE discontinuation is identical to IVD, same intended use as before
- Be bold and just continue with patient enrichment on own risk for non-compliance

➔ not pursued by Boehringer e.g. due to fear of loss of reputation

Option 2: Discontinue KL-6 based patient screening

Patient screening and inclusion criteria

- Patients are being screened for ESR, CRP and KL-6
- Each biomarker captures a distinct patient segment
- Patients with KL-6 levels ≥ 1000 U/ml are randomized into the study

- Comes with effort and costs
  - Protocol amendment at authorities required
  - Operational work such as site training, replacement of collection kits at sites

➔ not pursued by Boehringer study team in order to continue to select patients with a potential risk of disease progression

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Option 3: Talk to regulators I

1) Can RUO-labeled KL-6 kits be used to enrich remaining patients in ongoing trial (Immediate solution)?

Federal Institute for Drugs and Medical Devices

National competent authority

- Federal Institute for Drugs and Medical Devices (BfArM) not responsible to grant Boehringer toleration for RUO assay utilization
- To be discussed with competent local authority responsible for the lab oversight and thus, of lab which uses the test kit

Bezirksregierung Düsseldorf

Local competent authority

- District government declined as utilization of a RUO kit in this clinical trial would exceed the scope of research and development activities.
- Toleration cannot be granted

Option 3: Talk to regulators II

2) Can a Special Dispensation for a non-registered product be requested?

Federal Institute for Drugs and Medical Devices

National competent authority

- Article 54 IVDR is not admissible as there is no public health or patient safety interest here (only possible with „high medical need“)
- would only be applicable in Germany but not any other EU country
- Full Technical Documentation needed

Bezirksregierung Düsseldorf

Local competent authority

- Suggestion to apply for a Special Dispensation
- Must be granted by national competent authority

Option 3: Talk to regulators III

3) Can an in-house IVD be developed at a CRO acting as Health Institution (Long-term solution)? In the interim, can RUO assay be used for enrichment while CRO completes the formalities for in-house IVD?

Federal Institute for Drugs and Medical Devices

National competent authority

- Re-confirmed that under the IVDR there is an exemption for Health Institutions to develop an in-house IVD for medical use [Art. 5(5) IVDR]
- Health Institution would then be responsible for the test
- Usage of RUO assay ad interim out of BfArMs area of responsibility

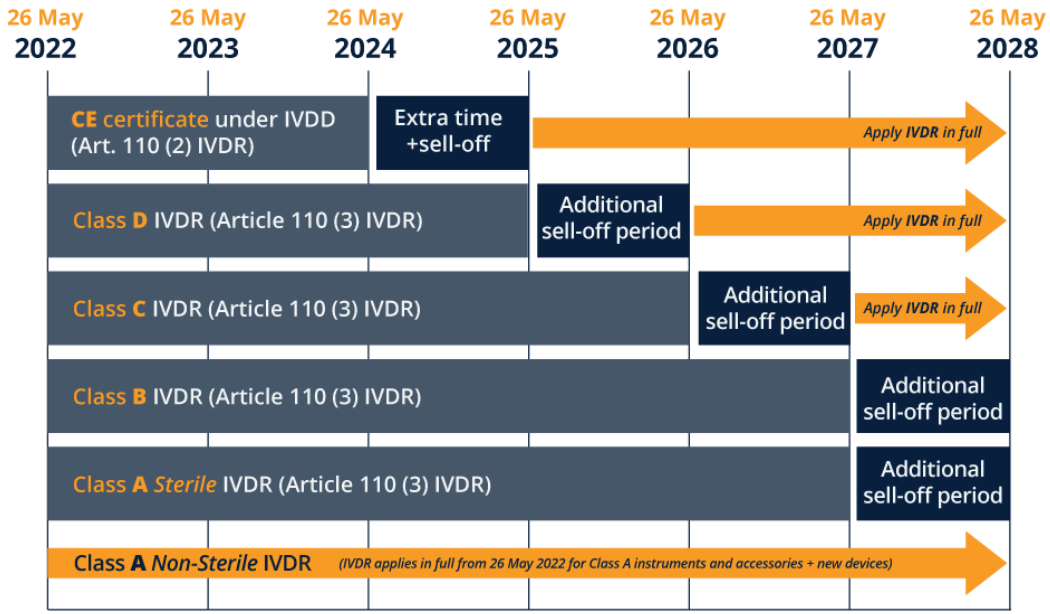
Bezirksregierung Düsseldorf

Local competent authority

- In-house IVD is a valid option to proceed after fulfillment of formal IVDR requirements
- Seek BfArM advice if in-house IVD is acceptable
- No toleration of RUO assay can be granted
- Discuss option of transitional provision with manufacturer

Option 4: Talk to the KL-6 kit manufacturer - transitional provision

- According to IVDR almost all products have to undergo a conformity assessment procedure with a notified body in accordance with IVDR classification rules.
- Transitional provision period is granted by EC
  - IVDs can be placed on the market and made available under Directive 98/79/EC (IVDD) depending on certificate status and classification of the IVD
  - Since May 26, 2022, manufacturer must still comply with IVDR provisions on post-market surveillance, vigilance, and registration of economic operators and of devices (EUDAMED). Foreign company must have an authorized representative.
- KL-6 IVD: Declaration of Conformity issued under IVDD before May 26, 2022 (no CE certificate by notified body)
  - qualified for continued sales of IVDD CE-labeled assay until May 26, 2027



Qserve

➔ not pursued by manufacturer

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Option 4: Talk to the KL-6 manufacturer – IVDR re-certification

- Provide support to re-certify IVD assay under IVDR in different ways depending on needs
- Resume CE-IVD production as soon as possible

Financial

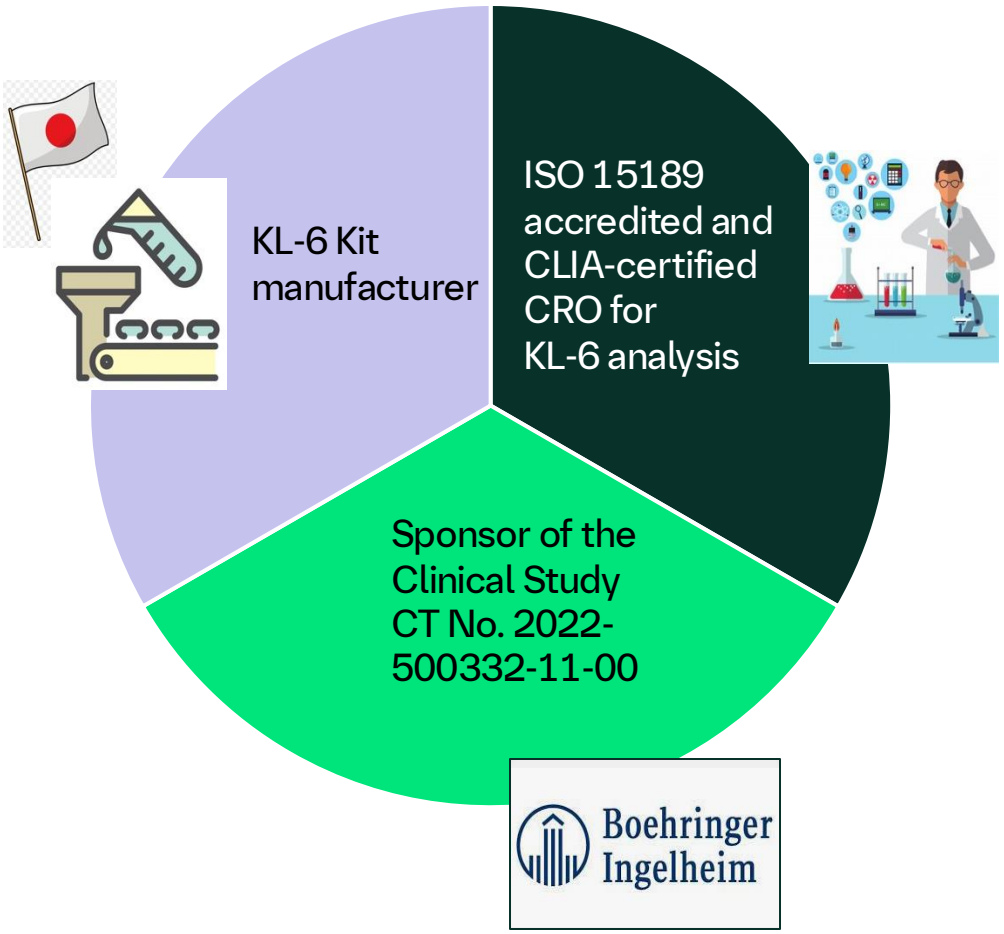
Regulatory knowledge

Capacities

➔ not pursued by manufacturer

Option 5: Health institution approach - in-house IVD based on the RUO kit from the Japanese manufacturer

- Involve a third party acting as a Health Institution (CRO in Germany)
- Gap analysis at CRO performed with external consultant
  - Qualification as Health Institution and of KL-6 assay as in-house IVD
    - Set-up quality agreement for KL-6 kits with Japanese manufacturer
    - Define intended use of in-house IVD
    - Update risk management system at CRO
    - Establishment of a lot-release process and set-up SOP(s) for surveillance of assay release
    - Compiling of IVDR compliant performance report on KL-6 assay
    - Declaration in accordance with Article 5(5)(f) IVDR



➔ in-house IVD available in Mar 2024, patient screening based on Kl-6 biomarker resumed immediately after

Option 6: Switch to another CE-labeled KL-6 IVD assay

- Extensive search performed (Google, AI, literature, EUDAMED,…)
- 2 potential assays identified but additional steps needed to leverage the assay for patient screening in the clinical study
  - Registered under 98/79/EC (IVDD) -> will assay be re-certified under IVDR by manufacturer?
  - New assay requirements unknown and method comparison to existing data necessary
  - Switch of matrix due to CE-certified intended use
- What if in-house IVD is performing better than CE-labeled assay?

European Commission | EN English | Search | Search

EUDAMED - European Database on Medical Devices

Home | Actors | Devices/SPPs | Certificates | News

Home > Devices/SPPs

Devices/Systems/Procedure packs

Search criteria

Model/Name: kl-6 ✕ | Status: On the EU market ✕ | New search

9 records found.

UDI-DI/ EUDAMED ID	Version	Basic UDI-DI/ EUDAMED DI	Trade name	Risk class	Manufacturer/Producer (and Authorised Representative) name	Actor ID/SRN	Action
04560189213593	1 (Current)	B-04560189213593		IVD General	Tosoh Corporation (Tosoh Europe N.V.)	JP-MF-000024143 (BE-AR-000000211)	
04560189213609	1 (Current)	B-04560189213609		IVD General	Tosoh Corporation (Tosoh Europe N.V.)	JP-MF-000024143 (BE-AR-000000211)	

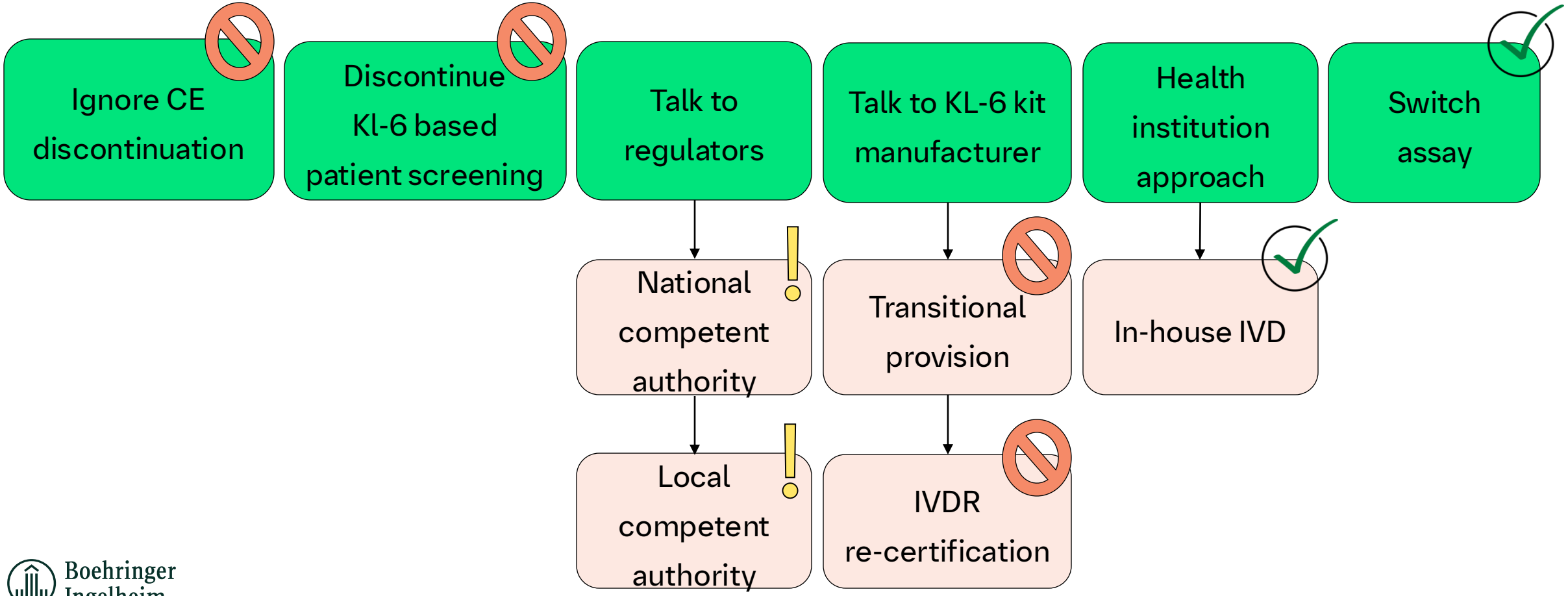
Devices/SPPs - EUDAMED (europa.eu)

➔ parallel approach to in-house IVD as long-term solution

Summary

Short-term solution: in-house IVD

Long-term solution: assay switch



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Intended Use – commercial assay vs. Inhouse IVD

	IVD_GER	RUO_GER
Commercial assay	2FT05TE *In Vitro* Diagnostic Use **INTENDED USE** For *in vitro* diagnostic use with the [redacted] System for the quantitative measurement of a sialylated carbohydrate antigen, KL-6 in human serum or plasma. This product is for professional use only.	B34155 v0 For research use only. Not for use in diagnostic procedures. **INTENDED USE** For research use with the automated [redacted] System for the quantitative measurement of a sialylated carbohydrate antigen, KL-6 in human serum or plasma. This product is not for use in diagnostic procedures, for 'Research Use Only'. This product is for professional use only.
In-house IVD	***INTENDED USE*** The [redacted] KL-6 is an in vitro diagnostic immunoassay intended for the quantitative determination of the sialylated carbohydrate antigen, KL-6 in human serum or plasma, as a supportive biomarker for prognosis of disease progression in adult subjects with Interstitial Lung Diseases (ILDs), either idiopathic or related to connective tissue diseases.	

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Intended Use – alternative assay

NAME AND INTENDED USE

[redacted] KL-6 TEST CUP is a single use reagent, designed for IN VITRO DIAGNOSTIC USE ONLY, by healthcare professionals, for the quantitative measurement of KL-6 in human serum or heparinised plasma, using the automated [redacted] Analyzers.

- currently certified under IVDD, but KL-6 is expected to be re-certified under IVDR in 2024.
- Different matrix than used in previous studies.